IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 3649
de la MONTE *et al.*	Art Unit: 1635
Appl. No. 09/964,678	Examiner: Whiteman, B.
Filed: September 28, 2001	Atty. Docket: 0609.4370002/RWE/FRC
For: **Transgenic Animals and Cell Lines for Screening Drugs Effective for the Treatment or Prevention of Alzheimer's Disease**	

Reply Brief Under 37 C.F.R. § 1.193(b)(1)

Mail Stop Appeal Brief - Patents

Commissioner for Patents
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Sir:

Appellants filed a Brief on Appeal to the Board of Patent Appeals and Interferences for the above-captioned application on October 8, 2003. The appeal is directed to the final rejections of claims 7-9, 14-16 and 35-40 under 35 U.S.C. § 112, first paragraph, as set forth in the Office Action dated April 8, 2003. The Examiner's Answer was mailed December 19, 2003. In reply to the Examiner's Answer, Appellants submit this Reply Brief Under 37 C.F.R. § 1.193(b)(1).

I. Related Appeals and Interferences

It was noted in the Appeal Brief that Appellants' undersigned representative was not aware of any appeals or interferences related to this application. *See* Appeal Brief at page 2. However, on December 15, 2003, subsequent to the filing of the Appeal Brief, a

Notice of Appeal was filed in U.S. Patent Application No. 09/380,203, which is the parent of the above-captioned application.

II. Grouping of the Claims

The Examiner disagreed with the grouping of the claims on the issue of enablement. *See* Examiner's Answer, page 14. According to the Examiner, "[a]ll of the pending claims are rejected under enablement for making and/or using the claimed transgenic animal." *See* Examiner's Answer, page 14.

Appellants maintain that the grouping of the claims, set forth at page 6 of the Appeal Brief, was proper. The Examiner has presented two distinct bases for the enablement rejection, neither of which can properly be applied to all of the claims. The first basis relates to the ability of a skilled artisan to obtain a DNA molecule that is at least 90% homologous to SEQ ID NO:1 and that codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. *See* Paper No. 16, pages 7-8. The second basis relates to the ability of a skilled artisan to make and use transgenic animals that exhibit a specific phenotype. *See* Paper No. 16, pages 9-14. As explained in the Appeal Brief at page 8, lines 1-17, the two bases for the enablement rejection cannot properly be applied to all of the claims. Thus, the claims do not stand or fall together. The grouping of the claims was proper.

Moreover, Appellants note that it is their prerogative to determine what claims stand or fall together and that the Examiner's opinion on this issue should be given no weight by the Board.

III. Written Description

Appellants have demonstrated that the USPTO's Synopsis of Written Description Guidelines ("Written Description Synopsis") specifically supports Appellants' position that the claimed subject matter is adequately described in the specification. *See* Appeal Brief at pages 12-18. Examples 14 and 9 of the Written Description Synopsis describe situations that are analogous to the circumstances surrounding the claims on appeal.

The Examiner has dismissed Appellants' assertions regarding the Examples in the Written Description Synopsis. It appears that the Examiner has not considered the general analytical guidance provided by the Written Description Synopsis relative to the present claims. Rather, the Examiner has simply pointed to particular differences in the details of the Examples as compared to the circumstances surrounding the claims on appeal.

First, the Examiner noted that Example 14 relates to variants of a protein that are at least 95% identical to SEQ ID NO:3, while the present claims include DNA molecules that are at least 90% homologous to SEQ ID NO:1. *See* Examiner's Answer at pages 15-16. Appellants maintain that the reasoning applied in Example 14, finding that the claimed subject matter is adequately described, would equally apply to the claims on

appeal, even though the particular details of the hypothetical scenario in Example 14 are not identical to those associated with the claims on appeal.

The Examples in the Written Description Synopsis are intended to serve as general guides for assessing compliance with 35 U.S.C. § 112, first paragraph. They do not set any absolute rules or numerical cut-offs. There is no indication in Example 14 that 95% identity is an essential factor in finding the written description requirement satisfied.

Example 14 discusses four factors as contributing to a finding of adequate written description:

(1) The claim in the example specifies an activity of the protein and a degree of sequence identity relative to a recited sequence;

(2) There is actual reduction to practice of a single species encompassed by the claim;

(3) Procedures for making variants of the claimed protein with a specific degree of sequence identity and that retain the recited activity are conventional in the art; and

(4) The specification describes an assay that will identify other species of the invention.

For each of these factors, there is an analogous factor that has been satisfied for the claims involved in this appeal. *See* the Appeal Brief at pages 14-16.

There is no indication in Example 14 that claims reciting less than 95% identity should be rejected under § 112, first paragraph, when all of the factors that were described as being important to a finding of adequate written description have been met. The analytical process that is applied in Example 14 should apply to the claims on appeal, even though the claims on appeal recite "at least 90% homologous," rather than "95% identity."

The second difference noted by the Examiner is that "Example 14 is directed to a protein that catalyzes a specific reaction and the instant claims do not recite a protein that catalyzes a specific reaction." *See* Examiner's Answer at page 16. Again, the Examiner has pointed to a specific difference that does not influence the underlying reasoning that was applied in the analysis of Example 14.

Example 14 relates to a claim directed to a protein that catalyzes the reaction of A→B. The important feature of the claim in Example 14, for purposes of assessing written description, is that it recites an *activity* of the protein, not that the protein catalyzes "A→B." Indeed, the fact that the generic reaction "A→B" is used in the Example shows that the reasoning applied in the Example is not intended to be limited to claims reciting any particular reaction or activity. Rather, A→B was intended to represent any distinguishing activity of the protein.

Independent claim 7 of this appeal specifies that the DNA molecule that is at least 90% homologous to SEQ ID NO:1 *codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells*. Just as a person of ordinary skill in the art would be able to determine if a given protein catalyzes the reaction of A→B, and thus

would be able ascertain whether a given protein falls within the scope of the claim of Example 14, a person of ordinary skill in the art would likewise be able to determine if a given DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. From the standpoint of assessing compliance with the written description requirement, having an activity of AD7c-NTP when over-expressed in neuronal cells is equivalent to catalyzing the reaction of A→B.

The Examiner also stated that "the as-filed specification does not provide sufficient description for procedures for making variants of SEQ ID NO:1, which has 90% homology and retains an activity of AD7c-NTP when over-expressed in neuronal cells." *See* Examiner's Answer at page 16. This is an incorrect assertion. As noted in the Appeal Brief at pages 21-23, the specification provides exemplary methods for obtaining DNA molecules which are at least 90% homologous to SEQ ID NO:1. The specification also describes methods for determining whether a DNA molecule that is at least 90% homologous to SEQ ID NO:1 codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. *See* the Appeal Brief at pages 22-23.

Example 14 of the Written Description Synopsis notes that "procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art." Likewise, procedures for making DNA molecules which are at least 90% homologous to SEQ ID NO:1 and which code for proteins that retain the activity of AD7c-NTP are conventional in the art. *See* Appeal Brief at page 15. Thus, this aspect of Example 14, which supported a conclusion of adequate written description, is also satisfied for the claims on appeal.

Finally, with respect to Example 9 of the Written Description Synopsis, the Examiner stated that:

> Example 9 is directed to an isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. The DNA molecule set forth in the claimed invention is not directed to a nucleic acid that encodes a protein that binds a receptor and stimulates a specific activity.

Examiner's Answer at page 17. Appellants submit that, even though the claim in Example 9 is not identical to the claims on appeal, the reasoning applied in Example 9 is equally applicable to the claims on appeal. The analysis presented in Example 9 leads to the conclusion that the written description requirement is fully satisfied for the claims on appeal.

In Example 9, the written description requirement was found to be satisfied, not because the claimed nucleic acid encoded a protein that binds to a receptor, but because: (a) techniques for identifying nucleic acid molecules encompassed by the claim were routine in the art, and (b) a person of ordinary skill in the art would not have expected substantial variation among the species encompassed by the claim. Similarly, as noted in the Appeal Brief, techniques for identifying DNA molecules that are at least 90% homologous to SEQ ID NO:1 were routine in the art, and persons of ordinary skill in the art would not expect substantial variation among DNA molecules that are at least 90% homologous to SEQ ID NO:1. *See* Appeal Brief at pages 17-18. Thus, notwithstanding

the particular differences in details noted by the Examiner, the analysis used in Example 9 would lead to the conclusion that the claims on appeal are adequately described.

When the analytical framework of Examples 14 and/or 9 of the USPTO's Written Description Synopsis is applied to the circumstances of the claims on appeal, it must be concluded that the claims on appeal are adequately described. In rejecting Appellants' assertions with respect to the guidance provided by the Written Description Synopsis, the Examiner has simply pointed to differences in specific details. The differences in details noted by the Examiner, however, do not change the underlying reasoning that was applied in the Examples. Thus, it was improper for the Examiner to dismiss Appellants' arguments regarding Examples 14 and 9 without considering the overall parallels between the circumstances in the Examples and the circumstances surrounding the claims on appeal.

IV. Enablement

A. A Person of Ordinary Skill in the Art Could Have Made and Used the DNA Molecules of the Transgenic Animals of the Invention without Undue Experimentation

One of the bases of the enablement rejection is the Examiner's assertion that it would have required undue experimentation for a skilled artisan to obtain a DNA molecule that is at least 90% homologous to SEQ ID NO:1 and that codes for a protein that has an activity of AD7c-NTP when overexpressed in neuronal cells. As demonstrated in the Appeal Brief at pages 21-23, a person of ordinary skill in the art

could have made and used the DNA molecules of the transgenic animals of the invention using only routine methods.

In response to Appellants' statements regarding enablement, the Examiner has set forth a mathematical argument based on the (supposed) total number of possible peptides having 375 amino acids. According to the Examiner, the total number of 375 amino acid peptides is 8.475×10^{65}. *See* Examiner's Answer at page 17. The Examiner also stated that "the as-filed specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen 8.475×10^{65} amino acid peptide for peptides that meet or do not meet the limitations set forth in the claims." *See* Examiner's Answer at page 18. The Examiner's mathematical argument does not support a finding of non-enablement because a person of ordinary skill in the art would not have needed to make and test every possible 375 amino acid polypeptide in order to obtain the DNA molecules included in the transgenic animals of the invention.

The germ and somatic cells of the transgenic animals of the invention comprise either the DNA molecule of SEQ ID NO:1 or a DNA molecule that is at least 90% homologous to SEQ ID NO:1. It is specified in claim 7 that the DNA molecule encodes a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. Thus, the enablement issue, insofar as it relates to DNA molecules included in the transgenic animals of the invention, is simply whether or not it would have required undue experimentation to: (a) obtain a DNA molecule that is at least 90% homologous to SEQ ID NO:1, and (b) determine if the DNA molecule, when overexpressed in neuronal

cells, codes for a protein having an activity of AD7c-NTP when over-expressed in neuronal cells.

As noted in the Appeal Brief, a skilled artisan could have obtained DNA molecules that are at least 90% homologous to SEQ ID NO:1 using only routine methods. *See* Appeal Brief at pages 21-22. For example, as described in the specification at page 19, lines 3-15, DNA molecules that are at least 90% homologous to SEQ ID NO:1 can easily be obtained by hybridizing DNA molecules from a cDNA library to the DNA molecule of SEQ ID NO:1 under stringent conditions. Once obtained, the DNA molecules could have easily been tested for the ability to code for proteins that have an activity of AD7c-NTP when over-expressed in neuronal cells. *See* Appeal Brief at page 22-23. Contrary to the Examiner's position, a skilled artisan would not have needed to make and test every possible 375 amino acid polypeptide in order to obtain a DNA molecule that is at least 90% homologous to SEQ ID NO:1 and that codes for a protein that has and activity of AD7c-NTP when over-expressed in neuronal cells.

The Examiner asserted that Sambrook *et al.* (submitted as Exhibit 3 with the Appeal Brief) actually supports the enablement rejection. *See* Examiner's Answer at page 19. The Examiner quoted two sentences from Sambrook to support this assertion: "at present, it is impossible to predict with accuracy the effect of substituting one amino acid for another in a protein;" and "when the number of desired mutants exceeds 20 or so, it becomes impractical and expensive to generate each of them individually."

Appellants submit that Sambrook does not provide any support for the enablement rejection. Sambrook sets forth a general problem in the art by noting that "it

is impossible to predict with accuracy the effect of substituting one amino acid for another in a protein." Sambrook also notes that using individual oligonucleotides to replace more than 20 amino acids with several other amino acids is impractical. The remainder of the Sambrook reference, however, describes methods that can be used to circumvent these technical issues. In particular, Sambrook describes methods for creating many mutations in a segment of DNA instead of producing multiple mutations individually. As noted in the Appeal Brief at page 22, the methods of Sambrook would have been available to persons of ordinary skill in the art prior to the effective filing date of the present application in order to generate DNA molecules that are at least 90% homologous to SEQ ID NO:1.

Sambrook, therefore, does not support the enablement rejection. Rather, Sambrook indicates that, despite the problems associated with predicting the effects of particular amino acid substitutions on protein function, it was nonetheless possible to create many mutants in a DNA molecule using routine methods. Such methods could have been used to create large numbers of DNA molecules that are at least 90% homologous to SEQ ID NO:1 and that could have easily been screened for those that code for proteins that have an activity of AD7c-NTP when over-expressed in neuronal cells.

The Examiner stated that "if you replace the nucleotide at each wobble position in the polynucleotide sequence set forth in SEQ ID NO: 1, the polynucleotide sequence would not have at least 90% sequence identity to SEQ ID NO: 1, but would have 100% amino acid sequence identity." *See* Examiner's Answer at page 21. Appellants

respectfully submit that this is an incorrect (and logically inconsistent) statement. Replacing a *nucleotide* at a wobble position in SEQ ID NO:1 would certainly produce a *DNA sequence* that is at least 90% homologous to SEQ ID NO:1. It is true that, by definition, the *amino acid* sequence would be the same. However, regardless of the fact that the *amino acid* sequence is the same, the *DNA* sequence is not identical but is in fact at least 90% homologous to SEQ ID NO:1.

Finally, according to the Examiner, "Appellants' assertion (pages 32-33) that screening for molecules that possess a particular activity (AD7c-NTP activity) is both common and routine in the biological arts is not supported by any evidence." *See* Examiner's Answer at page 21. Appellants note that screening DNA molecules for those that encode a protein with AD7c-NTP activity requires a skilled artisan to do only two things: (1) transfect neuronal cells with DNA molecules (under the control of a promoter), and (2) identify transfected cells that exhibit the cellular phenotypes associated with AD7c-NTP overexpression. Transfecting cells and observing their cellular phenotypes were routine procedures in the art. In addition, the specification describes both the transfection of cells with DNA molecules of the invention, and the identification of cells that exhibit the phenotypes caused by AD7c-NTP overexpression. *See* specification at page 45, line 16, through page 46, line 26. Since these two processes are all that are needed to screen DNA molecules for those that encode a protein with AD7c-NTP activity, it must be concluded that such screening would have been regarded as common and routine in the biological arts.

B. A Person of Ordinary Skill in the Art Could Have Made and Used the Transgenic Non-Human Animals of the Invention Without Undue Experimentation

1. Claims 7-9, 14-16, 35, 36, 39 and 40 do not Require that the Transgenic Animals Exhibit a Specific Phenotype

The enablement rejection, insofar as it relates to the production of transgenic animals, is based to a large extent on the Examiner's interpretation of the claims as requiring that the transgenic animals "[express] the protein at a level sufficient to result in a specific phenotype." Paper No. 16, page 11, line 10. Appellants noted in the Appeal Brief that claims 7-9, 14-16, 35, 36, 39 and 40 do not require that the transgenic animals exhibit a specific phenotype, and that transgenic animals encompassed by or included within the subject matter of claims 7-9, 14-16, 35, 36, 39 and 40 are useful in, *e.g.*, drug screening applications even if the animals do not exhibit any specific phenotypes. *See* Appeal Brief at pages 34-37.

The Examiner rejected the above arguments, simply stating that "[t]he specification does not teach that the claimed transgenic animal without a phenotype correlates to an animal model for Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas." *See* Examiner's Answer at page 24. Appellants note that independent claim 7 does not a recite "an animal model for Alzheimer's disease, neuroectodermal tumor, malignant astrocytomas, and glioblastomas." In addition, there is nothing in the specification that would indicate that the transgenic animals of the invention must exhibit any particular phenotype. According to the specification, "[t]he invention also relates to transgenic non-human animals which comprise the DNA

construct of the invention in each of its germ and somatic cells and which over express AD7c-NTP." *See* specification at page 20, lines 1-3. There is no mention of any phenotypes that *must* be exhibited by the animals.

Moreover, the specification clearly indicates that the transgenic animals of the invention are useful even if they do not exhibit any particular phenotype. For instance, the specification indicates that the transgenic animals may be used for determining if a candidate drug, when administered to the animals, causes, *e.g.*, the suppression or prevention of expression of the protein (encoded from the transgene), or the increased degradation of the protein. *See* specification at page 21, lines 3-20. A person of ordinary skill in the art would appreciate that, in order to detect the suppression or prevention of expression of the protein, or the increased degradation of the protein, the transgenic animals need not express any phenotype. As noted in the Appeal Brief at page 37, the only characteristic that the transgenic animals encompassed by or included within the subject matter of claims 7-9, 14-16, 35, 36, 39 and 40 need to possess in order to be useful for the contemplated screening methods is that they express the DNA molecule of SEQ ID NO:1 or a DNA molecule that is at least 90% homologous thereto.

Therefore, the Examiner has not made a cogent argument as to why it is believed that claims 7-9, 14-16, 35, 36, 39 and 40 require that the transgenic animals exhibit any specific phenotype. Most of the arguments set forth by the Examiner to support the position that making the transgenic animals of the invention would have required undue experimentation are based on the interpretation of the claims as requiring that the transgenic animals exhibit a particular phenotype. Since this is an incorrect

interpretation of the claims, the Examiner's arguments are irrelevant to the enablement analysis of claims 7-9, 14-16, 35, 36, 39 and 40.

2. The Examples in the Art Demonstrating the Successful Production of Transgenic Animals Indicate that It Would Not Have Required Undue Experimentation to Produce the Transgenic Animals of the Present Invention

Appellants have cited many examples in the scientific literature of the successful production of transgenic animals with specific phenotypes, including transgenic animals that exhibited neurological phenotypes indicative of Alzheimer's disease. *See* Appeal Brief at pages 27-29. The methods used to produce the transgenic animals in these examples would have been available to persons of ordinary skill in the art at the time of the effective filing date of the present application. Since others in the art were able to routinely produce transgenic animals having specific phenotypes, there is no reason to believe that persons of ordinary skill in the art would not have also been able to produce the transgenic animals of the present invention without undue experimentation.

In response, the Examiner stated that "the argument is not found persuasive because each of the exhibits use distinct materials not contemplated or taught by the instant specification." *See* Examiner's Answer at page 28. If by "distinct materials" the Examiner means different transgenes, Appellants agree that the cited references do not teach transgenic animals that fall within the scope of the present claims. Nonetheless, the general methodologies used in the references could have been applied in the context of the present invention. The mere fact that the references cited by Appellants involved the use of transgenes that are distinct from those of the present invention does not

suggest that the methods described in these references could not have been used to successfully produce the transgenic animals of the invention.

Appellants maintain that the Examiner has not presented any legally sufficient evidence or arguments that would indicate that making and using the transgenic animals of the invention would have required undue experimentation, especially since producing transgenic animals in general was routine in the art as of the effective filing date of the application. Thus, a *prima facie* case of non-enablement has not been established.

The remaining comments set forth in the Examiner's Answer are repetitive of those that have already been presented in the Office Actions and have been fully addressed in the Appeal Brief.

V. Conclusion

In light of the arguments above, as well as those set forth in Appellants' Brief on Appeal filed October 8, 2003, Appellants respectfully submit that the final rejections of claims 7-9, 14-16 and 35-40 under 35 U.S.C. § 112, first paragraph, are improper and should be reversed.

Respectfully submitted,

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